

# PATENT COOPERATION TREATY

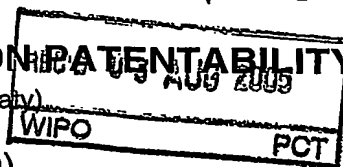
# PCT


## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

3 AUG 2005



Applicant's or agent's file reference SMC 60598/WO		<b>FOR FURTHER ACTION</b>		See Form PCT/IPEA/416
International application No. PCT/GB2004/002478		International filing date (day/month/year) 09.06.2004	Priority date (day/month/year) 13.06.2003	
International Patent Classification (IPC) or national classification and IPC C07C209/14, C07C209/16, C07B57/00, C07C211/27, C07C309/66, C07C29/143				
Applicant AVECIA PHARMACEUTICALS LIMITED ET AL.				
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 8 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input type="checkbox"/> sent to the applicant and to the International Bureau) a total of sheets, as follows:</p> <p><input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>				
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the opinion</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input checked="" type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input checked="" type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input type="checkbox"/> Box No. VIII Certain observations on the international application</p>				
Date of submission of the demand  15.11.2004		Date of completion of this report  03.08.2005		
Name and mailing address of the international preliminary examining authority:  European Patent Office - Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840		Authorized Officer  Rufet, J  Telephone No. +49 30 25901-		



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**Box No. I Basis of the report**

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1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
- ☐ international search (under Rules 12.3 and 23.1(b))
  - ☐ publication of the international application (under Rule 12.4)
  - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements\*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

**Description, Pages**

1-24 as originally filed

**Claims, Numbers**

1-22 as originally filed

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing
3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
  - ☐ the claims, Nos.
  - ☐ the drawings, sheets/figs
  - ☐ the sequence listing *(specify):*
  - ☐ any table(s) related to sequence listing *(specify):*
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages
  - ☐ the claims, Nos.
  - ☐ the drawings, sheets/figs
  - ☐ the sequence listing *(specify):*
  - ☐ any table(s) related to sequence listing *(specify):*

\* If item 4 applies, some or all of these sheets may be marked "superseded."

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**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

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1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:
- ☐ the entire international application,
  - ☒ claims Nos. 18-20  
because:
    - ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):
    - ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
    - ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
    - ☒ no international search report has been established for the said claims Nos. 18-20
    - ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
      - the written form ☐ has not been furnished
      - ☐ does not comply with the standard
      - the computer readable form ☐ has not been furnished
      - ☐ does not comply with the standard
    - ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
  - ☐ See separate sheet for further details

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**Box No. IV Lack of unity of invention**

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1. ☒ In response to the invitation to restrict or pay additional fees, the applicant has:
- ☐ restricted the claims.
  - ☐ paid additional fees.
  - ☐ paid additional fees under protest.
  - ☒ neither restricted nor paid additional fees.
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is
- ☐ complied with.
  - ☒ not complied with for the following reasons:  
**see separate sheet**
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☐ all parts.
  - ☒ the parts relating to claims Nos. 1-17,21,22 .

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**Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

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1. Statement

Novelty (N)	Yes: Claims	2-17,22
	No: Claims	1,21
Inventive step (IS)	Yes: Claims	10,17
	No: Claims	1-9,11-16
Industrial applicability (IA)	Yes: Claims	1-17,21,22
	No: Claims	

2. Citations and explanations (Rule 70.7):

**see separate sheet**

**Re Item III.**

A non-unity objection has been raised during the search stage. The Applicant has not paid extra fees, therefore no search report has been issued for the subject-matter of the claims 18-20.

Consequently no opinion will be given for the subject-matter of these claims.

**Re Item IV.**

The ISA found multiple inventions in this application as follow:

Invention I (claims 1-17,21,22)

Process for the preparation of an amine of formula (1) wherein an intermediate compound having a leaving group OL is reacting with ammonia and mesylate intermediates thereof

Invention II (claim 18)

Alternative process for the preparation of a stereoisomer of an alcohol compound of formula (14)

Invention III (claims 19,20)

Alternative process for the diastereomeric salt resolution of (S)-1-naphthylethylamine and diastereomeric salt thereof

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

The inventions listed above a priori do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The special technical feature which defines the contribution of invention I over the prior art is, according to the applicant, the specific sequence of steps (a), (b) and (c). It is pointed out that compounds of formula (1) are well known compounds e.g. (S)-1-(1-naphthyl)ethylamine, RN: 10420-89-0).

The special technical feature of invention II is the step of reducing a ketone of formula (6) into the corresponding stereoisomer alcohol of formula (14); it is also stressed that compounds of formulae (14) and (6) are well known compounds, e.g. RN: 15914-84-8,

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RN: 42177-25-3, RN: 941-98-0.

The special technical feature of invention III is to carry out the resolution of the known (S)-1-naphthylethylamine using tartaric acid or (S)-chloropropionic acid.

Moreover it is pointed out that according to the PCT Gazette-Section IV, (g)(v), a requirement for unity is that the intermediate and the final products shall not be separated, in the process leading from one to the other, by an intermediate which is not novel, which is not the case in the present application.

Due to the fact that no other technical features can be regarded as special technical feature in the sense of rule 13.2 PCT, the ISA is of the opinion that there is no single inventive concept underlying the 3 inventions in the sense of rule 13.1 PCT.

Since the Applicant did not paid additional search fees the examination has been limited to the first invention mentioned.

**Re Item V.**

1. The following documents are referred to in this communication:

- D1: J. ORG. CHEM., vol. 42, no. 18, 1977, pages 3101-3103, XP002300103
- D2: J. MED. CHEM., vol. 44, no. 21, 2001, pages 3343-3346, XP002300104
- D3: WO 00/66558 A
- D4: US 6 391 865 B1.
- D5: WO 98/42643 A cited by Applicant
- D6: US 5 767 276 A cited by Applicant
- D7: WO 99/24410 A cited by Applicant
- D8: J. HETEROCYCLIC CHEM., vol. 26, 1989, pages 269-275, XP002300105
- D9: JP 2001 294568 A
- D10: WO 86/01502 A
- D11: DATABASE CROSSFIRE BEILSTEIN; Database-Accession no. 4377580 (ID) XP002300107
- D12: TETRAHEDRON LETTERS, vol. 43, no. 34, 2002), pages 5993-5995,
- D13: J.A.C.S, vol. 114, no. 10, 1992, pages 3943-3950, XP002300106

## **2. Novelty**

2.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1 is not new in the sense of Article 33(2) PCT in view of the teaching of D1.

Document D1 discloses a process for the preparation of a primary amine (1-phenylethylamine derivative) falling under formula (1) of present claim 1 comprising the steps (a), (b) and © as claimed; see especially page 3102, column 2.

2.2 A process for the preparation of a 1-naphthylethylamine compound of formula (5) according to claims 2-17, comprising the steps (a), (b) and (c) is not described in the prior art documents D1-D10.

Documents D2-D4, D8-D10 refer to the preparation of 1-phenylethylamine derivatives instead of 1-naphthylethylamine derivatives (see D2, scheme 2; D3, p. 80-81; D4, p. 9, scheme 2; D8, scheme I; D9, abstract; D10, example 2)

Documents D5-D7 refer to the reducing step (a) as claimed.

2.3 Compound claims 21, 22

D11-13 disclose mesylate compounds falling under the scope of formula (15) of claim 21 and are therefore novelty destroying documents for claim 21.

the compound of formula (16) of claim 22 appears to be novel over the prior art.

## **3. Inventive step**

3.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject matter of claims 2-9, 11-16 does not involve an inventive step in the sense of Article 33(3)PCT.

3.2 Documents D1-D4 are considered to represent equally the most relevant state of the art to the subject matter of claim 2, because each of these documents discloses an analogy process of the process of claim 2, which differs only by the nature of the starting compound i.e 1-phenylethylamine derivative instead of a 1-naphthylethylamine derivative.

3.3 The subject-matter of claim 2 differs from the disclosure of D5-D7 in that only the catalytic reduction of a naphthyl ketone of formula (6) (step (a)) as claimed is disclosed.

3.3 The problem to be solved by the present invention may therefore be regarded as the provision of an alternative process for the preparation of 1-naphthylethylamine

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compounds as well as enantiomers thereof.

In view of D1-D4 the solution proposed in claim 2 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT), because the claimed process is an analogy process using a different known starting ketone. Furthermore the skilled person already knows from D5-D7 that 1-naphthyl ethyl alcohol of formula (7) or (9) can be produced from the 1-acetonaphthone in high enantiomers selectivity (see especially D6, table I and D7, table 2, entry 14).

Therefore the features disclosed in D5-D7 and D1-4 would be combined by the skilled person, without exercise of any inventive skills in order to solve the problem posed.